This document is an **Interagency Science Discussion/Final Agency Review** draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe PDF Format (xxx pp, xxM). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to EPA's PDF page for instructions.

Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

Substance Code: XXXX

Hexachloroethane (CASRN: 67-72-1); 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgrd.html .

STATUS OF DATA FOR Hexachloroethane

File First On-Line 00/00/0000

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

__I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Hexachloroethane

CASRN – 67-72-1

Section I.A. Last Revised – 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfD values can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

A previous oral RfD of 1×10^{-3} mg/kg-day for hexachloroethane was posted on the IRIS database in 1987.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure	UF	Chronic RfD
Atrophy and degeneration of renal tubules Rat Subchronic Dietary Study Gorzinski et al., 1985	$BMDL_{10}$ of 0.728 mg/kg-day	1000	7×10^{-4} mg/kg-day

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Data on the health effects of oral hexachloroethane exposure in humans are not available. The oral exposure database for hexachloroethane includes a 103-week gavage study in F344 rats (NTP, 1989), a 78-week gavage study in Osborne-Mendel rats (NCI, 1978), a 91-week gavage study in $B6C3F_1$ mice (NCI, 1978), a 16-week feeding study in F344 rats (Gorzinski et al., 1985), and a 13-week gavage study in F344 rats (NTP, 1989). In addition, the oral exposure database for hexachloroethane includes several acute (Kinkead and Wolfe, 1992; Weeks et al., 1979; Weeks and Thomasino, 1978; Reynolds, 1972; Fowler, 1969) and short-term (NTP, 1996; NTP 1989; Weeks et al., 1979) studies. The acute and short-term study data were not considered in the selection of the principal study for the derivation of the RfD because the database contains dose-response data from studies of subchronic and chronic durations.

However, short-term studies in rats (NTP, 1996, 1989) were used to support findings in the subchronic and chronic studies.

The available subchronic and chronic oral exposure studies for hexachloroethane identified kidney or liver effects associated with exposure to hexachloroethane. Reported effects include tubular nephropathy (NTP, 1989; NCI, 1978), atrophy and degeneration of renal tubules (NTP, 1989; Gorzinski et al., 1985), slight hypertrophy and/or dilation of proximal convoluted renal tubules (Gorzinski et al., 1985), linear mineralization of renal tubules (NTP, 1989), hyperplasia of the renal pelvic transitional epithelium (NTP, 1989), and hepatocellular necrosis (NTP, 1989). Given the number and greater sensitivity of kidney effects in available studies, the kidney was considered the primary target of oral hexachloroethane exposure toxicity in rodents. Therefore, kidney effects were further considered as candidate critical effects for the determination of the point of departure (POD) for derivation of the oral RfD.

The most sensitive effect observed in male rats exposed to hexachloroethane is slight hypertrophy and/or dilation of proximal convoluted renal tubules (Gorzinski et al., 1985), although the candidate POD for slight hypertrophy and/or dilation of proximal convoluted renal tubules (i.e., 0.710 mg/kg-day) is nearly identical to the candidate POD for atrophy and degeneration of renal tubules (i.e., 0.728 mg/kg-day). Tubular nephropathy in the chronic studies was characterized as atrophy and degeneration of renal tubules (NTP, 1989; NCI, 1978), indicating that this kidney effect has been consistently observed following hexachloroethane exposure in several studies. Therefore, atrophy and degeneration of renal tubules was selected as the candidate critical effect for male rats exposed to hexachloroethane.

The subchronic Gorzinski et al. (1985) study reported the most sensitive POD for atrophy and degeneration of renal tubules in male rats, with a $BMDL_{10}$ of 0.728 mg/kg-day, compared to 16.99 mg/kg-day and 2.60 mg/kg-day for the tubular nephropathy reported in the NCI (1978) and NTP (1989) chronic studies, respectively. The ability of the chronic studies (NCI, 1978; NTP, 1989) to inform the effects observed at the lowest dose tested in the Gorzinski et al. (1985) study is limited. In the chronic studies, the lowest dose tested represented a LOAEL and Gorzinski et al. (1985) did not provide severity data for comparison with NTP (1989). Therefore, the Gorzinski et al. (1985) study was selected as the principal study and atrophy and degeneration of renal tubules in male rats was selected as the critical effect.

In the Gorzinski et al. (1985) study, hexachloroethane was administered (in feed) to groups of 10 male and 10 female F344 rats at doses of 0, 1, 15, or 62 mg/kg-day for a period of 16 weeks. Kidney effects consisted of slight hypertrophy and/or dilation of proximal convoluted renal tubules and atrophy and degeneration of renal tubules. Slight hypertrophy and/or dilation of the proximal convoluted renal tubules was not observed in the control rats of either sex or in hexachloroethane exposed female rats. EPA determined that increases in slight hypertrophy and/or dilation of the proximal convoluted renal tubules were statistically significant in male rats treated with 15 or 62 mg/kg-day hexachloroethane (see Table 5-1). Atrophy and degeneration of renal tubules was observed in both male and female rats. EPA determined that increases in incidences of atrophy and degeneration of renal tubules were statistically significant in male rats treated with 15 or 62 mg/kg-day hexachloroethane and in female rats fed 62 mg/kg-day hexachloroethane (see Table 5-1). The authors concluded that the no-observed-effect level (NOAEL) for both male and female rats was 1 mg/kg-day. EPA considered the male rat lowest-observed-adverse-effect level (LOAEL) as 15 mg/kg-day and the male rat NOAEL as 1 mg/kg-day, based on

increased incidence of the renal tubule effects. EPA considered the female rat LOAEL as 62 mg/kg-day and the female rat NOAEL as 15 mg/kg-day, based on increased incidence of renal tubule effects.

Methods of Analysis. The benchmark dose (BMD) modeling approach (U.S. EPA, 2000b) was employed to identify the candidate POD for atrophy and degeneration of renal tubules (Gorzinski et al., 1985) and tubular nephropathy (NCI, 1978; NTP, 1989). Atrophy and degeneration of renal tubules in male F344 rats from the Gorzinski et al. (1985) study provided the POD for deriving the RfD.

___I.A.3. UNCERTAINTY FACTORS

$UF = 1000 = 10\ (UF_A) \times 10\ (UF_H) \times 3\ (UF_S) \times 1\ (UF_L) \times 3\ (UF_D)$

A default interspecies UF (UF_A) of 10 was applied to account for the variability in extrapolating from rats to humans. Although the toxicokinetics have been minimally evaluated in animals, the toxicokinetics of HCE have not been sufficiently characterized in either rats or humans to identify the active compound or determine dose metrics.

A default intraspecies UF (UF_H) of 10 was applied to adjust for potentially sensitive human subpopulations in the absence of information on the variability of response to HCE in the human population. Current information is unavailable to assess human-to-human variability in HCE toxicokinetics and toxicodynamics.

The study selected as the principal study was a 16-week study by Gorzinski et al (1985), a study duration that is minimally past the standard subchronic (90-day) study and falls well short of a standard lifetime study (i.e., two year chronic bioassay). Some data (NTP, 1989; Gorzinski et al., 1985; NCI, 1978) are available to inform the nature and extent of effects that would be observed with a longer duration of exposure to HCE. The chronic data identify the kidney is the target organ of HCE toxicity, consistent with the findings from the Gorzinski et al. (1985) study. In addition, data from the NCI (1978) chronic study suggest that an increase in duration of HCE exposure may not increase the incidence of nephropathy. As the Gorzinski et al. (1985) study did not report severity data for the renal effects, there are insufficient data to exclude the possibility that chronic exposure could increase the severity of the observed kidney effects. However, increases in severity of tubular nephropathy in the NTP (1989) chronic study was reported at similar doses as atrophy and degeneration of renal tubules in the Gorzinski et al. (1985) subchronic study, suggesting consistency in dose response relationships between chronic and subchronic studies. For these reasons, a subchronic-to-chronic UF (UF_S) of 3 was used to account for the extrapolation from subchronic-to-chronic exposure duration.

An UF for a LOAEL to a NOAEL extrapolation was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% increase in the incidence of renal tubule atrophy and degeneration was selected under an assumption that it represents a minimal biologically significant change.

An UF of 3 was applied to account for deficiencies in the HCE toxicity database, including the lack of a multigenerational reproductive study. The database includes studies in laboratory animals, including chronic and subchronic dietary exposure studies and two oral developmental toxicity studies. Therefore, in consideration of the oral database for HCE, a database UF of 3 was applied to account for the lack of a two-generational reproductive study.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

The predominant noncancer effect of acute, short-term, subchronic, and chronic oral exposure to hexachloroethane is renal toxicity. The acute and short-term study data were not considered in the selection of the principal study for the derivation of the RfD because the database contains dose-response data from studies of subchronic and chronic durations. In addition to the Gorzinski et al. (1985) study, two chronic studies in rats (NTP, 1989; NCI, 1978), a chronic study in mice (NCI, 1978), and a subchronic study in rats (NTP, 1989) support the selection of the kidney as the target organ and atrophy and degeneration of renal tubules as the critical effect of hexachloroethane exposure.

In the NTP (1989) chronic study, hexachloroethane was administered via gavage at doses of 7 and 14 mg/kg-day in male F344 rats and 57 and 114 mg/kg-day in female F344 rats for 103 weeks. Nephropathy (characterized by tubular cell degeneration and regeneration, tubular dilatation and atrophy, glomerulosclerosis, interstitial fibrosis, and chronic inflammation) was observed in hexachloroethane-treated rats of both sexes. Nephropathy was also reported in control rats of both sexes. Although a high incidence of nephropathy was observed in control rats, the study authors reported that the incidence of more severe nephropathy increased in dosed rats relative to controls (NTP, 1989). EPA considered the increase in severity of nephropathy in male rats by analyzing the incidence of greater than mild nephropathy. EPA determined that the increased incidence of moderate or marked nephropathy in males was statistically significant at the 14 mg/kg-day dose (see Table 5-1). EPA considered the increased severity of nephropathy in female rats by analyzing the incidence of nephropathy that was greater than minimal nephropathy. EPA determined that the increased incidences of mild to moderate nephropathy were statistically significant in females at the 57 and 114 mg/kg-day doses (see Table 5-1). Linear mineralization of the renal papillae and hyperplasia of the renal pelvic epithelium were increased in a dose-dependent, statistically significant manner in the treated male rats. EPA determined that the increased incidences of linear mineralization of the renal papillae and hyperplasia of the renal pelvic epithelium were statistically significant in males at the 7 and 14 mg/kg-day doses (see Table 5-1). The increased severity of nephropathy and dose-dependent increases in the incidence of mineralization of the renal papillae and hyperplasia of renal pelvic transitional epithelium in male rats suggests that hexachloroethane exposure exacerbated the nephropathy observed in the NTP (1989) study. The NTP (1989) chronic study did not identify NOAELs for male or female rats as kidney effects were observed at the lowest doses tested. EPA considered the male rat LOAEL as 7 mg/kg-day based on increased incidence in moderate or marked tubular nephropathy (characterized by degeneration, necrosis, and regenerative epithelial cells), hyperplasia of the pelvic transitional epithelium, and linear mineralization of the renal papillae in the NTP (1989) study. EPA considered the female rat LOAEL as 57 mg/kg-day, based on dose-related increases in incidence and severity of nephropathy in the NTP (1989) study.

In the NCI (1978) chronic rat study, hexachloroethane was administered via gavage to groups of 50 male and 50 female Osborne-Mendel rats for 5 days/week, cyclically for 66 of the 78 weeks, followed by an observation period of 33–34 weeks (total of 112 weeks). The TWA doses of hexachloroethane were 113 and 227 mg/kg-day. Tubular nephropathy was observed in all groups of treated animals, but was not observed in either untreated or vehicle controls. Statistically significant increases in incidence of tubular nephropathy were observed at 113 and 227 mg/kg-day hexachloroethane in both male and female rats (see Table 5-1). The NCI (1978) study did not identify a NOAEL for tubular nephropathy in rats. EPA considered the LOAEL as 113 mg/kg-day, based on a dose-related increase in incidence of nephropathy in both male and female rats.

In the NCI (1978) chronic mouse study, hexachloroethane was administered via corn oil gavage to groups of 50 male and 50 female B6C3F_1 mice for 5 days/week for 78 weeks followed by an observation period of 12–13 weeks (total of 90 weeks). Starting in week 9, the hexachloroethane doses were increased, though no explanation for the increase was provided. The TWA doses of hexachloroethane were 360 and 722 mg/kg-day. Because of low survival rates in the vehicle and untreated male control groups, NCI (1978) compared tumor incidences in the dosed males and females to the pooled vehicle control data derived from concurrently run bioassays for several other chemicals. NCI (1978) reported chronic kidney inflammation (i.e., tubular nephropathy characterized by degeneration of the convoluted tubule epithelium at the junction of the cortex and medulla and hyaline casts) in male and female B6C3F_1 mice administered 360 and 721 mg/kg-day hexachloroethane. EPA considered the LOAEL for this study as 360 mg/kg-day based on tubular nephropathy, while a NOAEL could not established from these data.

In the NTP (1989) subchronic study, hexachloroethane was administered via gavage to groups of 10 male and 10 female F344 rats at TWA doses of 0, 34, 67, 134, 268, and 536 mg/kg-day for 13 weeks. Kidney effects (i.e., hyaline droplet formation, renal tubular regeneration, and renal tubular casts) were observed in male rats from all hexachloroethane exposure groups, though incidence data were only provided for the 34 mg/kg-day dose group. NTP (1989) reported that the severity of kidney effects in male rats increased with dose, but no data on severity were presented. No kidney effects were reported in female F344 rats exposed to hexachloroethane. Liver effects were observed in male and female rats at higher doses of hexachloroethane and EPA determined that statistically significant increases in hepatocellular necrosis were observed in female rats exposed to 268 or 536 mg/kg-day hexachloroethane (see Table 5-1).

For more detail on Susceptible Populations, exit to the Toxicological Review, Section 4.8 (PDF).

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study - High

Data Base – Low to Medium

RfD – Low to Medium

Overall confidence in the RfD is low to medium. Confidence in the principal study, Gorzinski et al. (1985), is high. The 16-week study is a well-conducted study that used three dose groups plus a control. NTP (1989) also conducted 16-day, 13-week, and 103-week studies that supported the results observed in the 16-week study. Application of BMD modeling provided a POD upon which to base the derivation of the RfD. The critical effect on which the RfD is based is well-supported by other oral short-term, subchronic, and chronic studies. Confidence in the database is low to medium because the database includes acute, short-term, subchronic, and chronic toxicity studies and developmental toxicity studies in rats and chronic carcinogenicity bioassays in rats and mice. The database lacks a multigenerational reproductive study and studies in other species.

For more detail on Characterization of Hazard and Dose Response, exit to the Toxicological Review, Section 6 (PDF)

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document – (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hexachloroethane* (U.S. EPA, 2011). **To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).**

___I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

__I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name - Hexachloroethane

CASRN – 67-72-1

Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. A summary of the evaluation of potential human carcinogenicity of hexachloroethane is contained in Section II of this file.

An inhalation assessment for hexachloroethane was not previously available on IRIS.

__I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure	UF	Chronic RfC
Neurotoxicity	$NOAEL_{[HEC]}$ of 83 mg/m^3	3000	3×10^{-2} mg/m^3
Rat Subchronic Inhalation Study			
Weeks et al., 1979			

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

The database of inhalation toxicity studies on hexachloroethane is limited. Human studies demonstrated hexachloroethane exposure in smoke bomb production workers, but the sample sizes are too small to reach definitive conclusions regarding health effects and the exposure was likely a mixture of hexachloroethane and zinc oxide. There are no chronic inhalation studies available. The inhalation exposure database for hexachloroethane consists of an acute study in rats (Weeks and Thomasino, 1978) and a subchronic inhalation study in four species that included a developmental toxicity experiment (Weeks et al., 1979).

Weeks et al. (1979) exposed male, female, and pregnant female Sprague-Dawley rats (21-25/sex/concentration) to control air, 15, 48, or 260 ppm hexachloroethane (145, 465, and 2,517 mg/m^3, respectively; purity 99.8%) for 6 hours/day, 5 days/week for 6 weeks. Postexposure observation was

carried out for 12 weeks. An oxygen consumption test was also conducted. The authors reported that in the 2,517 mg/m^3 group, body weight gain of male rats, but not the nonpregnant female rats, was reduced beginning in the third week of exposure (although quantitative information was not reported). All rats in the 2,517 mg/m^3 group exhibited tremors, ruffled pelt, and red exudates around the eyes following the fourth week of exposure. The authors reported that in the male rats, relative kidney, spleen, and testes weights were significantly increased; in the female rats, only relative liver weights were significantly increased (although quantitative information was not reported). One male and one female rat in the 2,517 mg/m^3 exposure group died during the fourth week, but the authors did not report a cause of death. During the postexposure observation period, treatment-related effects disappeared. No gross changes were evident at necropsy after the 12 week postexposure observation period; however, male and nonpregnant female rats of the 2,517 mg/m^3 group sacrificed immediately after the 6 week inhalation exposure had a higher incidence and severity of mycoplasma-related lesions in nasal turbinates, trachea, and lung compared with controls. The authors concluded that these lesions were related to potentiation of an endemic mycoplasia infection rather than a direct effect of hexachloroethane exposure [U.S. EPA considered "mycoplasia" a typographical error in the Weeks et al. (1979) study. In subsequent discussion, the Toxicological Review will refer to this data as "mycoplasma"]. However, no data were presented demonstrating the presence of mycoplasma in the lung. There were no histopathological differences observed between control and exposed rats sacrificed 12 weeks postexposure. No treatment-related effects were observed in the rats exposed to 145 and 465 mg/m^3 hexachloroethane.

In the oxygen consumption test, male rats (5/concentration) were tested prior to and following exposure to 145, 465, or 2,517 mg/m^3 hexachloroethane for 15 minutes, 3 days/week for the duration of the study (6 weeks). The 2,517 mg/m^3 rats exhibited significantly decreased mean rates of consumption prior to (15%) and after (13%) exposure to hexachloroethane. The authors suggested that this decrease in oxygen consumption, while nonspecific, is indicative of an alteration in basal metabolic rate. No histopathological effects were observed at this concentration. EPA considered 465 mg/m^3 the NOAEL and 2,517 mg/m^3 the LOAEL, based on reduced body weight gain, and increased organ weights.

Weeks et al. (1979) also exposed male Sprague-Dawley rats (15/concentration) to 15, 48, or 260 ppm hexachloroethane (145, 465, or 2,517 mg/m^3) for 6 hours/day, 5 days/week for 6 weeks and examined them for behavioral changes related to learned and unlearned responses (described in detail in Section 4.4.3.2). Similar to the other treated rats, body weight gain was reduced. Final mean body weight gain in male rats was reduced 2, 5, and 10% (statistically significant) in the 145, 465, and 2,517 mg/m^3 dose groups, respectively, compared with controls. Additionally, relative lung, liver, kidney, and testes weights were increased (quantitative information not reported) compared with controls.

Weeks et al. (1979) also exposed four male Beagle dogs/concentration to control air, 15, 48, or 260 ppm hexachloroethane (145, 465, and 2,517 mg/m^3, respectively; purity 99.8%) for 6 hours/day, 5 days/week for 6 weeks. Postexposure observation was carried out for 12 weeks. Blood samples were evaluated for blood chemistry parameters. In addition, the dogs underwent pulmonary function tests prior to and following exposure. One dog died within 5 hours of exposure to 2,517 mg/m^3. The remaining animals in the 2,517 mg/m^3 group exhibited signs of neurotoxicity consisting of tremors, ataxia, hypersalivation, head bobbing, and facial fasciculations. No blood parameters were significantly affected and no exposure-related histopathological lesions were observed following necropsy on dogs sacrificed 12 weeks postexposure. Dogs evaluated for pulmonary functions while anesthetized did not display any significant effects. The hexachloroethane-exposed dogs did not display any treatment-related toxicity at

12 weeks postexposure. EPA considered 465 mg/m^3 the NOAEL and 2,517 mg/m^3 the LOAEL, based on neurotoxic effects.

Weeks et al. (1979) also exposed male Hartley guinea pigs (10/concentration) to control air, 15, 48, or 260 ppm hexachloroethane (145, 465, and 2,517 mg/m^3, respectively; purity 99.8%) for 6 hours/day, 5 days/week for 6 weeks. Postexposure observation was carried out for 12 weeks. Guinea pigs were also evaluated for sensitization potential following inhalation exposure to hexachloroethane. Two guinea pigs died during each of the fourth and fifth weeks, resulting in four total deaths. Guinea pigs of the 2,517 mg/m^3 group displayed reductions in body weight beginning at the second week of exposure and significantly increased liver to body weight ratios (quantitative information was not reported). No treatment-related effects were observed in the other exposure groups. EPA considered the NOAEL as 465 mg/m^3 and the LOAEL as 2,517 mg/m^3, based on decreased body weight and significantly increased relative liver weight.

Weeks et al. (1979) also exposed male and female quail (*C. japonica,* 20/concentration) to control air, 15, 48, or 260 ppm hexachloroethane (145, 465, and 2,517 mg/m^3, respectively; purity 99.8%) for 6 hours/day, 5 days/week for 6 weeks. Postexposure observation was carried out for 12 weeks. The only observed effect was excess mucus in nasal turbinates in 2/10 quail in the 2,517 mg/m^3 group after 6 weeks. The authors considered the excess mucus to be transient based on the lack of any inflammation or histopathological effects. Although the study authors considered the excess mucus to be a transient effect, EPA notes that the lack of inflammation and histopathological effects does not preclude the presence of more sensitive indicators of immune response (e.g., antibodies or other immune signaling chemicals) unable to be detected with methods available to the study authors. EPA considered 2,517 mg/m^3 (highest exposure concentration) as the NOAEL, while the LOAEL could not be established from this study.

The subchronic inhalation study by Weeks et al. (1979), as the only repeated exposure study available, was selected as the principal study for the derivation of the RfC. The Weeks et al. (1979) study is a well-conducted subchronic bioassay which used three concentrations and incorporated a variety of endpoints (e.g., toxicological, teratological, neurological, pulmonary) across a range of species (see Table 5-4). The authors evaluated portal of entry effects by gross examination of lungs, trachea, and nasal turbinates following necroscopy on animals that died during the study or were sacrificed at 12 weeks postexposure. In addition, Weeks et al. (1979) evaluated upper respiratory effects by examining histological sections of the nasal turbinates and evaluated upper respiratory inflammation by the presence of polymorphonuclear leukocytes in close association with excess mucus within the lumens of the nasal passages. The primary limitation of Weeks et al. (1979) is the minimal amount of quantitative information provided characterizing the reported effects. Several experiments only utilized one sex, and additional exposure concentration(s) between the mid- and high concentration would have allowed for better characterization of the exposure-response curve. However, this study identified neurotoxicity, statistically significant decreases in body weight gain, and upper and lower respiratory tract irritation. The responses were generally observed following exposure to the highest concentration, and not in the two lower concentrations. Considering the consistent observation of neurotoxic effects across experiments in rats and dogs, these effects following inhalation exposure to hexachloroethane were selected as the critical effect.

Methods of Analysis. Neurological effects were observed in male and female Sprague-Dawley rats, male Beagle dogs, and pregnant Sprague-Dawley rats only at the highest dose tested. Incidence data were not

reported, which precluded application of BMD modeling. Therefore, the NOAEL of 465 mg/m^3 identified in Weeks et al. (1979) was selected as the POD for the derivation of the RfC based on effects in male and female rats and male dogs exposed to hexachloroethane for 6 weeks and pregnant rats exposed on GDs 6–16.

___I.B.3. UNCERTAINTY FACTORS

UF = 3000 = 3 (UF_A) × 10 (UF_H) × 10 (UF_S) × 1 (UF_L) × 10 (UF_D)

For animal-to-human interspecies differences (UF_A), a UF of 3 was applied to account for the uncertainty in extrapolating from laboratory animals to humans. This value is adopted by convention, where an adjustment from an animal-specific $NOAEL_{ADJ}$ to a $NOAEL_{HEC}$ has been incorporated. Application of an UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component associated with HCE is mostly addressed by the determination of an HEC as described in the RfC methodology (U.S. EPA, 1994b). Insufficient data exist to inform the toxicodynamic uncertainty component; therefore, an UF of 3 is retained to account for uncertainty regarding the toxicodynamic differences between rats and humans.

A default intraspecies UF (UF_H) of 10 was applied to account for potentially sensitive human subpopulations in the absence of information on the variability of response to HCE in the human population. Information is currently unavailable to assess human-to-human variability in HCE toxicokinetics and toxicodynamics.

The subchronic inhalation study by Weeks et al. (1979), as the only repeated exposure study available, was selected as the principal study. No chronic inhalation studies were identified for HCE; therefore, there are no data to inform the effects that might be observed with increased exposure duration. Therefore, a subchronic-to-chronic UF (UF_S) of 10 was applied to account for the use of the POD selected following a subchronic duration of exposure to HCE to estimate a chronic exposure RfC.

An UF for a LOAEL to a NOAEL extrapolation was not applied because this assessment utilized a NOAEL as the POD.

A 10-fold UF was used to account for deficiencies in the toxicity database for inhalation exposure to HCE. The toxicity data for inhalation exposure to HCE is limited and largely restricted to one subchronic (6-week) inhalation study (Weeks et al., 1979) in rats, male dogs, male rabbits, and quail. The same investigators performed a developmental study and an acute study in rats. Maternal toxicity was observed at both doses. Fetuses of HCE-treated dams did not exhibit any significant skeletal or soft tissue anomalies. The toxic effects observed in the dams in the developmental study were similar to those observed in the rats exposed for 6 weeks, although additional effects were observed in the rats exposed for a longer duration. The absence of teratogenic effects does not abrogate concern for other fetal effects, given that only developmental toxicity studies in a single species are available in the inhalation database for HCE. The database lacks a long-term study, and a multigeneration reproductive toxicity study. In addition, the database lacks studies of neurotoxicity and developmental neurotoxicity, endpoints of concern based on the available inhalation data. Therefore, in consideration of the inhalation database for HCE, a database UF of 10 was applied.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

The database of inhalation toxicity studies on hexachloroethane is limited to an subchronic inhalation study and an acute exposure study. The subchronic inhalation study by Weeks et al. (1979), as the only repeated exposure study available, was selected as the principal study for the derivation of the RfC. An acute study of inhalation exposure in rats (Weeks and Thomasino, 1978) provided support for effects observed in the Weeks et al. (1979) subchronic studies.

Weeks and Thomasino (1978) exposed six male rats/concentration (strain not specified, although one table in the report indicated strain as Sprague-Dawley) to 2,500 or 57,000 mg/m^3 hexachloroethane for 8 hours and to 17,000 mg/m^3 hexachloroethane for 6 hours. Postexposure observation was carried out for 14 days. Male rats exposed for 8 hours to 2,500 mg/m^3 hexachloroethane displayed no toxic signs during exposure or for 14 days thereafter. Body weight gain was slightly, but not statistically significantly, reduced over the 14-day exposure period. Male rats exposed for 8 hours to 57,000 mg/m^3 hexachloroethane displayed severe toxic signs including death. At 6 hours, one rat had a staggered gait. At 8 hours, 2/6 rats were dead. The surviving rats showed statistically significant reductions in mean body weight on exposure days 0 (7%), 1 (21%), 3 (19%), 7 (15%), and 14 (15%), compared with controls. Necropsy did not reveal any gross exposure-related lesions. Microscopy revealed that two of the four surviving rats had minimally to moderately severe subacute diffuse interstitial pneumonitis and vascular congestion. Additionally, a purulent exudate of the nasal turbinates was observed in one control and one treated rat. The authors concluded that this effect was not exposure-related, but rather was indicative of a low-grade endemic upper respiratory disease. The male rats exposed for 6 hours to 17,000 mg/m^3 showed slight reductions in body weight gain on postexposure days 1 (5%) and 3 (4%) and body weights similar to controls for the remaining 11 days of the postexposure period. Two of the six rats demonstrated a staggered gait. No exposure-related gross or histopathological changes were observed in tissues and organs.

For more detail on Susceptible Populations, exit to the Toxicological Review, Section 4.8 (PDF).

___I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study - Low

Data Base – Low

RfD – Low

Overall confidence in the RfC is low. Confidence in the principal study, Weeks et al. (1979), is low. The 6-week study was conducted in several species (including male dogs, male and female rats, male guinea pigs, and quail). The study used three exposure groups (145, 465, and 2,517 mg/m^3) plus a control. The study is limited by the relatively short exposure duration (6 weeks) and minimal reporting of effects, especially quantitative changes. Confidence in the database is low because the database includes one acute and one subchronic toxicity study in multiple species and one developmental toxicity study in rats. The database lacks studies by another laboratory and a multigenerational reproductive study.

For more detail on Characterization of Hazard and Dose Response, exit to the Toxicological Review, Section 6 (PDF)

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hexachloroethane* (U.S. EPA, 2011). **To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).**

___I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name - Hexachloroethane
CASRN – 67-72-1
Section II. Last Revised -- 00/00/0000

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A previous cancer assessment for hexachloroethane was posted on the IRIS database in 1987. At that time, hexachloroethane was classified as a C carcinogen (possible human carcinogen), based on the observation of carcinomas in one mouse strain following oral exposure to hexachloroethane. An oral cancer slope factor (CSF) of 1.4×10^{-2} mg/kg-day was derived from the tumor incidence data for hepatocellular carcinoma in male and female $B6C3F_1$ mice exposed to hexachloroethane by gavage for 78 weeks, followed by an observation period of 12-13 weeks after cessation of exposure (NCI, 1978). The linearized multistage extra risk procedure was used for extrapolation. A drinking water unit risk of 4×10^{-7} µg/L was derived. An inhalation unit risk (IUR) was not previously derived.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

In accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), hexachloroethane is characterized as "likely to be carcinogenic to humans." Although there are no available studies on cancer in humans exposed to hexachloroethane, chronic oral exposure bioassays in animals have reported (1) dose-dependent, statistically significant increases in the incidence of renal adenoma or carcinoma combined in male F344/N rats, (2) statistically significant increases in the incidence of pheochromocytomas/malignant pheochromocytomas combined in male F344/N rats (NTP, 1989), and (3) statistically significant increases in the incidence of hepatocellular carcinomas in male and female $B6C3F_1$ mice (NCI, 1978). Based on the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), data indicating cancer in more than one animal species, more than one sex, and more than one site of cancer support the cancer descriptor "likely to be carcinogenic to humans" for hexachloroethane.

The available evidence does not establish a mode of action (MOA) by which hexachloroethane induces renal adenomas and carcinomas. There are studies that indicate an α_{2u}-globulin MOA for the renal tumors observed male rats (NTP, 1989); however, two factors provide support for the conclusion that there are insufficient data to support an α_{2u}-globulin mode of action for the development of renal tumors. First, the presence of kidney effects in hexachloroethane-exposed male and female mice, which generally do not accumulate the α_{2u}-globulin protein, suggests a mode of action other than α_{2u}-globulin nephropathy. Second, none of the hexachloroethane studies performed the necessary immunohistochemical assays to confirm the presence of α_{2u}-globulin protein within the hyaline droplets observed following administration of hexachloroethane (NTP, 1996, 1989). The MOA by which hexachloroethane produces pheochromocytomas and hepatocellular carcinoma is unknown, and the available data do not support any hypothesized carcinogenic MOA for hexachloroethane.

For more detail on Characterization of Hazard and Dose Response, exit to the Toxicological Review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the Toxicological Review, Section 4.8 (PDF).

___II.A.2. HUMAN CARCINOGENICITY DATA

There are no available studies on cancer in humans associated with exposure to hexachloroethane.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Two chronic oral exposure bioassays provided evidence of carcinogenic effects following hexachloroethane exposure in rats and mice. NTP (1989) provided evidence of renal adenomas and carcinomas and pheochromocytomas and malignant pheochromocytomas in male F344/N rats in a 2-year cancer bioassay. NCI (1978) provided evidence of hepatocellular carcinomas in male and female $B6C3F_1$ mice in a 91-week cancer bioassay. Both NTP (1989) and NCI (1978) are well-designed studies, conducted in both sexes of two species with 50 animals/sex/dose. Each study utilized two dose groups of hexachloroethane and an untreated control group, with examination of a wide range of toxicological endpoints in both sexes of the rodents.

NTP (1989) conducted a chronic toxicity/carcinogenicity bioassay in F344/N rats. Groups of 50 male rats/dose were administered TWA doses of 7 and 14 mg/kg-day of hexachloroethane (purity >99%) by corn oil gavage, 5 days/week for 103 weeks. Groups of 50 female rats/dose were administered, by corn oil gavage, 5 days/week for 103 weeks, TWA doses of 57 and 114 mg/kg-day. Male rats exhibited a dose-related, statistically significant increase in the incidence of combined renal adenomas or carcinomas at the highest dose. Combined renal adenomas or carcinomas were observed in 2, 4, and 14% of controls, 7, and 14 mg/kg-day males, respectively. No hexachloroethane-related renal tumors were observed in female rats. The combined incidence of all three types of pheochromocytomas (benign, malignant, and complex pheochromocytomas) was statistically significantly increased in males treated with 7 mg/kg-day hexachloroethane (62%) and increased in males treated with 14 mg/kg-day (43%) when compared with vehicle controls (30%) and historical controls in the study laboratory (75/300; 25 ± 7%) and in NTP studies (543/1,937; 28 ± 11%). No hexachloroethane-related adrenal gland tumors were observed in female rats.

NCI (1978; Weisburger, 1977) conducted a chronic toxicity/carcinogenicity bioassay in Osborne-Mendel rats. hexachloroethane (purity >98%) at doses of 0, 250, or 500 mg/kg-day was administered by

corn oil gavage to 50 rats/sex/dose for 5 days/week for 78 weeks. Following termination of exposure, rats were observed for 33–34 weeks for a total duration of 111–112 weeks. Twenty rats/sex were used for the untreated and vehicle controls. Starting in week 23, rats in the exposure groups began a 5-week cyclic rotation that involved 1 week without exposure followed by dosing for 4 weeks. After adjustment from 5 days/week for 78 weeks, with the 5-week cyclic rotation for part of the time, to continuous exposure over the standard 2 years for a chronic bioassay, the TWA doses were 113 and 227 mg/kg-day. Mortality was increased in the 113 and 227 mg/kg-day males with survival rates of 24/50 (48%) and 19/50 (38%), respectively, compared with 14/20 (70%) in the untreated controls. Survival rates for the female rats were 14/20 (70%) for both the untreated and vehicle controls, and 27/50 (54%) and 24/50 (48%) for the 113 and 227 mg/kg-day dose groups, respectively. All of the tumor types observed had been encountered previously as spontaneous lesions in the Osborne-Mendel rat and no statistical differences in frequencies were observed between treated and control rats. NCI concluded that there was no evidence of carcinogenicity in this rat study. Notably, the doses used in the Osborne-Mendel rats of the NCI (1978) study were approximately 16 times greater than those doses administered to F344 male rats by NTP (1989).

NCI (1978; Weisburger, 1977) conducted a chronic toxicity/carcinogenicity bioassay in a $B6C3F_1$ mice. Hexachloroethane (purity >98%) was administered by corn oil gavage at TWA doses of 360 and 722 mg/kg-day for 5 days/week for 78 weeks, followed by 12–13 weeks of an observation period (total 91 weeks). Survival rates in males were 5/20 (25%), 1/20 (5%), 7/50 (14%), and 29/50 (58%) in the vehicle control, untreated control, and 360 and 722 mg/kg-day dose groups, respectively. Survival rates in females were 80, 85, 80, and 68% in vehicle control, untreated control, 360 and 722 mg/kg-day groups, respectively. Both male and female mice exhibited statistically significantly increased incidences of hepatocellular carcinomas. The treated males demonstrated an increased tumor response for hepatocellular carcinomas that was dose-related: 30 and 63% in the 360 and 722 mg/kg-day dose groups, respectively, compared with 10% in pooled vehicle controls and 15% in matched vehicle controls. Females demonstrated an increased tumor response that was not dose related in that a higher incidence of hepatocellular carcinomas occurred at the low dose (40%) compared with the high dose (31%); pooled vehicle and matched vehicle controls had incidences of 3 and 10%, respectively. NCI concluded that hexachloroethane was carcinogenic in both sexes of $B6C3F_1$ mice.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

In addition to the two chronic bioassays in rodents, evidence of hexachloroethane's promotion (following treatment with DEN), but not initiation, potential was observed in the liver of male Osborne-Mendel rats administered a single gavage dose of 497 mg/kg hexachloroethane (Milman et al., 1988; Story et al., 1986). Lattanzi et al. (1988) reported in vivo and in vitro binding of hexachloroethane to DNA, RNA, and protein in mice and rats. In both rats and mice administered single i.p. injections of 127 μCi/kg [^{14}C]-hexachloroethane, in vivo covalent binding of hexachloroethane for RNA was consistently much greater than that for DNA or protein. DNA exhibited the lowest amount of hexachloroethane binding. Species differences were evident for all three macromolecule types (DNA, RNA, and protein), with the mouse exhibiting much higher levels (9 times greater) of covalent binding for DNA in the liver than the rat. The binding was 2 and 3 times greater for mice than rats with RNA and protein, respectively, from the liver. The binding was similar between species, but slightly greater in mice, for the kidney, lung, and stomach analyses. In vitro covalent binding to DNA was observed at comparable levels in liver microsomes from both rats and mice following exposure to hexachloroethane. Kidney

microsomes from rats and mice produced statistically significantly greater amounts of DNA binding compared with controls, with greater amounts of DNA binding from mice (threefold increase) compared with rats (twofold increase). Microsomes from the lungs and stomachs in both species did not display increased DNA binding activity over corresponding controls.

In vivo genotoxicity studies have not been performed in humans exposed to hexachloroethane. In vivo exposure to animals resulted in predominantly negative results. Similarly, in vitro genotoxicity studies conducted in microorganisms, cultured mammalian cells, and insects were largely negative both in the presence and absence of exogenous metabolic activation.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor: 4×10^{-2} per mg/kg-day

The derivation of the oral slope factor 4×10^{-2} per mg/kg-day is based on the incidence of renal adenomas and carcinomas combined in male rats exposed to orally hexachloroethane in for 2 years using a low dose linear extrapolation in the absence of sufficient information to inform the MOA (NTP, 1989).

To derive the oral slope factor, the hexachloroethane doses administered to laboratory animals were scaled to human equivalent doses (HEDs) according to EPA guidance (U.S. EPA, 2005a, 1992). The dose metric used in the estimate of the HED is the applied or external dose of hexachloroethane because a PBPK model was unavailable. Using the calculated HEDs, the 2° multistage model in BMDS (version 2.0) (U.S. EPA, 2008) was fit to the incidence data. The multistage model was fit to the incidences of renal adenomas or carcinomas combined in male rats and hepatocellular carcinomas in male mice. The multistage model was also fit to the incidence of pheochromocytomas or malignant pheochromocytomas in male rats and the incidence of hepatocellular carcinomas in female mice. The model exhibited a significant lack of fit for the pheochromocytomas and hepatocellular carcinomas in female mice (according to the χ^2 statistic with $p < 0.1$). Thus, these datasets were not useful for dose-response assessment because the tumor incidences are not a monotonic increasing function of dose, as demonstrated by the Cochran-Armitage Trend Test. Therefore, the renal adenomas/carcinomas combined in male rats (NTP, 1989) and the hepatocellular carcinomas in male mice were used to derive candidate oral slope factors (see Table 5-6).

The candidate oral slope factors were derived by linear extrapolation to the origin from the POD by dividing the BMR by the $BMDL_{10}$ (the lower bound on the exposure associated with a 10% extra cancer risk). The oral slope factor represents an upper bound estimate on cancer risk associated with a continuous lifetime exposure to hexachloroethane. In accordance with the U.S. EPA guidelines (2005a), an oral slope factor for renal tumors in male rats of 0.04 $(mg/kg\text{-}day)^{-1}$ was calculated by dividing the BMR of 0.1 by the human equivalent $BMDL_{10}$ of 2.45 mg/kg-day (Appendix B). An oral slope factor for hepatocellular tumors in male mice of 0.007 $(mg/kg\text{-}day)^{-1}$ was calculated by dividing the BMR of 0.1 by the human equivalent $BMDL_{10}$ of 13.80 mg/kg-day (Appendix B). The rats exhibited greater sensitivity to hexachloroethane-induced carcinogenicity than the mice. Thus, the risk estimate associated with the male rats that developed renal adenomas or carcinomas was selected as the oral slope factor of 0.04 $(mg/kg\text{-}day)^{-1}$ for hexachloroethane. The slope of the linear extrapolation from the central estimate (i.e., BMD) is 0.1/37.03 mg/kg-day or 3×10^{-3} $(mg/kg\text{-}day)^{-1}$.

____II.B.1.2. Drinking Water Unit Risk*: 8.6×10^{-8} $(\mu g/L)^{-1}$

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	1166 µg/L
E-5 (1 in 100,000)	116.6 µg/L
E-6 (1 in 1,000,000)	11.7 µg/L

*The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

____II.B.1.3. Extrapolation Method

The multistage model in BMDS (version 2.0) (U.S. EPA, 2008) was fit to the incidence data summarized in Table 5-5 using the calculated HEDs in order to derive an oral slope factor for hexachloroethane. The BMR selected was the default value of 10% extra risk recommended for dichotomous models (U.S. EPA, 2000b). No data were excluded from the BMD multistage modeling.

The multistage model was fit to the incidences of renal adenomas or carcinomas combined in male rats and hepatocellular carcinomas in male mice. In all cases, the 2° multistage model provided the best fit. The multistage model was also fit to the incidence of pheochromocytomas or malignant pheochromocytomas in male rats and the incidence of hepatocellular carcinomas in female mice. The model exhibited a significant lack of fit for the pheochromocytomas and hepatocellular carcinomas in female mice (according to the χ^2 statistic with $p < 0.1$). Thus, these datasets were not useful for dose-response assessment because the tumor incidences are not a monotonic increasing function of dose, as demonstrated by the Cochran-Armitage Trend Test. Therefore, these datasets were not further considered in the derivation of the cancer slope factor.

___II.B.2. DOSE-RESPONSE DATA

Tumor Type – renal adenomas and carcinomas combined

Test Species – male F344 rats

Route – Oral

References – NTP (1989)

Summary of incidence data in rodents orally exposed to hexachloroethane for use in cancer dose-response assessment

Study	Sex/strain/species	Endpoint	Hexachloroethane dose (mg/kg-day)	Incidence
NTP (1989)	Male F344 rats	Renal adenoma or carcinoma	0	1/50 (2%)
			7.1	2/50 (4%)
			14.3	7/50 (14%)[a]

[a]Denotes statistical significance.

Summary of BMD modeling results for oral cancer assessment of hexachloroethane

Study	Sex/strain/ species	Endpoint	"Best-fit" model	BMR	BMD_{10}	$BMDL_{10}$ or POD	Oral slope factor $(mg/kg\text{-}d)^{-1}$
NTP (1989)	Male F344 rats	Renal adenomas/carcinomas combined	2° Multistage	0.1	3.74	2.45	0.04

___II.B.4. DISCUSSION OF CONFIDENCE

Relevance to humans. There are insufficient data to characterize the modes of action for the kidney (adenomas/carcinomas) and adrenal gland tumors (pheochromocytomas) in male rats and liver tumors (hepatocellular carcinomas) in male and female mice. There are some data in experimental animals evaluating α_{2u}-globulin accumulation and toxicity in the kidney. Two principal factors contribute to the conclusion that there are insufficient data to support an α_{2u}-globulin mode of action for the development of renal tumors. First, the presence of kidney effects in hexachloroethane-exposed male and female mice and female rats, which generally do not accumulate the α_{2u}-globulin protein, suggests a mode of action other than α_{2u}-globulin nephropathy. Second, none of the hexachloroethane studies performed the necessary immunohistochemical assays to confirm the presence of α_{2u}-globulin protein within the hyaline droplets observed following administration of hexachloroethane (NTP, 1996, 1989). This represents a data gap.

There is no available information regarding hepatic cancer associated with hexachloroethane exposure in humans. The experimental animal literature, however, shows that oral exposure to hexachloroethane induces liver tumors in male and female mice. It is possible that the hexachloroethane-induced hepatocellular carcinomas in mice occur as a result of the binding of hexachloroethane metabolites to liver macromolecules and the generation of free radicals during hexachloroethane metabolism, causing key events in the carcinogenic process such as cytotoxicity, inflammation, and regenerative cell proliferation. Limited information exists to distinguish the similarities and differences between experimental animals and humans in terms of hexachloroethane metabolism or toxicity. However, these potential key events have not been evaluated for hexachloroethane.

Pheochromocytomas are catecholamine-producing neuroendocrine tumors. The relevance of rodent pheochromocytomas as a model for human cancer risk has been the subject of discussion in the scientific literature (e.g., Greim et al., 2009; Powers et al., 2008). In humans, pheochromocytomas are rare and usually benign, but may also present as or develop into a malignancy (Eisenhofer et al., 2004; Lehnert et al., 2004; Elder et al., 2003; Goldstein et al., 1999). Hereditary factors in humans have been identified as important in the development of pheochromocytomas (Eisenhofer et al., 2004). Pheochromocytomas are more common in laboratory rats, though evidence suggests that certain rat pheochromocytomas may have similarity to human pheochromocytomas (Powers et al., 2009). Furthermore, mechanisms of action inducing pheochromocytomas in rats are expected to occur in humans as well (Greim et al., 2009).

In the absence of information indicating otherwise, the kidney and adrenal gland tumors in male rats and liver tumors in male and female mice are considered relevant to humans.

Choice of low-dose extrapolation approach. A linear-low-dose approach was used to estimate human carcinogenic risk associated with hexachloroethane exposure, in the absence of information to inform the dose-response at low doses. The extent to which the overall uncertainty in low-dose risk estimation could be reduced if the mode of action for hexachloroethane were known is of interest. It is possible that an α_{2u}-globulin-associated mode of action is, in fact, responsible for male rat tumor formation. In that case, the renal tumors would not have been utilized for quantitation of cancer risk as they would have been characterized as not relevant to humans.

Etiologically different tumor types were not combined across sites prior to modeling, in order to allow for the possibility that different tumor types can have different dose-response relationships because of varying time courses or other underlying mechanisms or factors. The human equivalent oral slope factors estimated from the tumor sites with statistically significant increases ranged from 0.007 to 0.04 per mg/kg-day, a range less than one order of magnitude, with greater risk coming from the male rat kidney data.

Interspecies extrapolation. An adjustment for cross-species scaling ($BW^{0.75}$) was applied to address toxicological equivalence of internal doses between each rodent species and humans, consistent with the U.S. EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It is assumed that equal risks result from equivalent constant lifetime exposures.

Choice of model. All risk assessments involve uncertainty, as study data are extrapolated to make inferences about potential effects in humans from environmental exposure. The largest sources of uncertainty in the hexachloroethane cancer risk estimates are interspecies extrapolation and low-dose extrapolation. There are no human data from which to estimate human cancer risk; therefore, the risk estimate must rely on data from studies of rodents exposed to levels greater than would occur from environmental exposures.

Without human cancer data or better mechanistic data, the relevance of the rodent cancer results to humans is uncertain. The occurrence of increased incidences of kidney and adrenal gland tumors in male rats, and liver tumors in male and female mice exposed to hexachloroethane from the oral route of exposure suggests that hexachloroethane is potentially carcinogenic to humans as well.

Regarding low-dose extrapolation, in the absence of mechanistic data for biologically based low-dose modeling or mechanistic evidence supporting a nonlinear approach (see the discussion at the beginning of Section 5.4.3) a linear low-dose extrapolation was carried out from the $BMDL_{10}$. It is expected that this approach provides an upper bound on low-dose cancer risk for humans. The true low-dose risks cannot be known without additional data.

With respect to uncertainties in the dose-response modeling, the two-step approach of modeling only in the observable range (U.S. EPA, 2005a) and extrapolating from a POD in the observable range is designed in part to minimize model dependence. Measures of statistical uncertainty require assuming that the underlying model and associated assumptions are valid for the data under consideration. The multistage model used provided an adequate fit to all the datasets for kidney and liver tumors. For the multistage model applied to the incidence of tumors, the BMDLs should generally be within a factor of 3 of the BMDs. This indicates that there is a reasonably typical degree of uncertainty at the 10% extra risk level. A large difference between the BMD and BMDL raises concern that the algorithm for the calculation of the BMDL is not accurate (U.S. EPA, 2000b). The ratios of the BMD_{10} values to the $BMDL_{10}$ values did not exceed a value of 2.6, indicating that the estimated risk is not influenced by any unusual variability in the model and associated assumptions.

Dose metric. Hexachloroethane is potentially metabolized to PERC and pentachloroethane; however, it is unknown whether a metabolite or some combination of parent compound and metabolites is responsible for the observed toxicity and carcinogenicity of hexachloroethane. If the actual carcinogenic moiety(ies) is(are) proportional to administered exposure, then use of administered exposure as the dose metric provides an unbiased estimate of carcinogenicity. On the other hand, if administered exposure is

not the most relevant dose metric, then the impact on the human equivalent slope factor is unknown. Consequently; the low-dose cancer risk value may be higher or lower than that estimated, by an unknown amount. In the absence of data identifying the carcinogenic moiety for hexachloroethane, the administered exposure was selected as the dose metric.

Bioassay selection. The study by NTP (1989) was used for the development of an oral slope factor. This study was conducted in both sexes of F344/N rats and used 50 male and 50 female rats per dose group. Test animals were allocated among two dose levels of hexachloroethane and an untreated control group. Animals were observed twice daily and examined weekly (for 14 weeks) then monthly for body weight and monthly for feed consumption. Animals were necropsied and all organs and tissues were examined grossly and microscopically for histopathological lesions for a comprehensive set of toxicological endpoints in both sexes.

Choice of species/gender. The oral slope factor for hexachloroethane was quantified using the tumor incidence data for male rats, which were found to be more sensitive than male or female mice to the carcinogenicity of hexachloroethane. The oral slope factor calculated from male rats was higher than the slope factors calculated from male and female mice. As there is no information to inform which species or gender of animals would be most applicable to humans, the most sensitive group was selected for the basis of the oral slope factor. Although there is insufficient evidence to characterize the mode of action for the observed kidney tumors in rodents, the evidence suggesting the kidney as a target organ of hexachloroethane toxicity in both species lends strength to the concern for human carcinogenic potential.

Human population variability. The extent of inter-individual variability or sensitivity to the potential carcinogenicity of hexachloroethane is unknown. There are no data exploring whether there is differential sensitivity to hexachloroethane carcinogenicity across life stages. In addition, neither the extent of interindividual variability in hexachloroethane metabolism nor human variability in response to hexachloroethane has been characterized. Factors that could contribute to a range of human responses to hexachloroethane include variations in CYP450 levels because of age-related differences or other factors (e.g., exposure to other chemicals that induce or inhibit microsomal enzymes), nutritional status, alcohol consumption, or the presence of underlying disease that could alter metabolism of hexachloroethane or antioxidant protection systems. This lack of understanding about potential susceptibility differences across exposed human populations thus represents a source of uncertainty. Humans are expected to be more genetically heterogeneous than inbred strains of laboratory animals (Calderon, 2000), and this variability is likely to be influenced by ongoing or background exposures, diseases, and biological processes.

____II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

In the absence of data on the carcinogenicity of hexachloroethane via the inhalation route, an inhalation unit risk has not been derived.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document – (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hexachloroethane* (U.S. EPA, 2011).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_III. [reserved]

_IV. [reserved]

_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name – Hexachloroethane

CASRN – 67-72-1

Section VI. Last Revised – 00/00/0000

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VII. REVISION HISTORY

Hexachloroethane

CASRN – 67-72-1

File First On-Line 03/31/1987

Date	Section	Description
09/30/1987	I.A.	Oral RfD assessment on-line
03/01/1988	I.A.5.	Confidence levels revised

03/01/1988	II.B.3.	Text clarified
03/01/1988	II.B.4.	Confidence statement revised
03/01/1988	II.C.4.	Confidence statement revised
01/01/1991	II.	Text edited
01/01/1991	II.C.1.	Inhalation slope factor removed (global change)
04/01/1991	I.A.	Text edited
04/01/1991	I.A.7.	Secondary contact changed
04/01/1991	II.	Text edited
04/01/1991	VI.	Bibliography on-line
12/01/1991	I.B.	Inhalation RfC now under review
12/01/1991	IV.F.1.	EPA contact changed
01/01/1992	IV.	Regulatory actions updated
12/01/1992	I.B.	Work group review date added
02/01/1994	II.D.3.	Secondary contact's phone number changed
08/01/1995	I.B.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
00/00/0000	I., II., VI.	RfD, RfC and cancer assessment updated.

_VIII. SYNONYMS

Substance Name – Hexachloroethane

CASRN – 67-72-1

Section VIII. Last Revised – 03/31/1987

- 67-72-1
- AVLOTHANE
- CARBON HEXACHLORIDE
- DISTOKAL
- DISTOPAN
- DISTOPIN
- EGITOL
- ETHANE HEXACHLORIDE
- ETHYLENE HEXACHLORIDE
- FALKITOL
- FASCIOLIN
- HEXACHLOR-AETHAN
- Hexachloroethane
- 1,1,1,2,2,2-HEXACHLOROETHANE
- HEXACHLOROETHYLENE
- MOTTENHEXE
- NA 9037
- NCI-C04604
- PERCHLOROETHANE
- PHENOHEP
- RCRA WASTE NUMBER U131